



A New Synthesis of Aziridine-2-carboxylates by Reaction of Hexahydro-1,3,5-triazines with Alkyldiazoacetates in the Presence of Tin(IV) Chloride¹

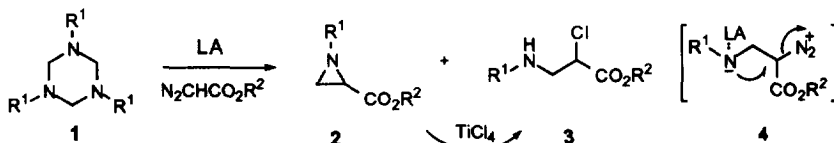
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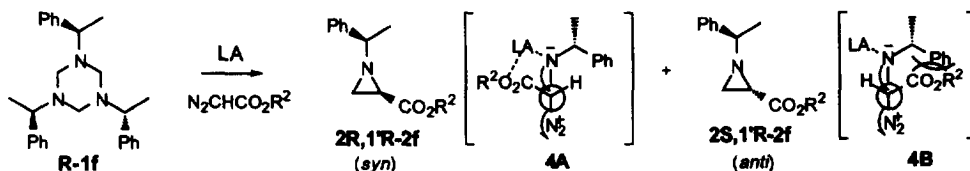
Abstract: Aziridine-2-carboxylates were prepared from the reaction of hexahydro-1,3,5-triazines with alkyldiazoacetates in the presence of Lewis acid catalyst in high yield.

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Aziridine-2-carboxylates attract great attentions as useful building blocks for the synthesis of α - and β -amino esters, β -lactams and alkaloids.² A few synthetic methods were reported based on three different approaches, a) nucleophilic displacement of nitrogen with removal of the leaving group at α -position³, b) 1,2-addition of nitrogen to olefins⁴ and c) 1,2-addition of carbon by imines⁵. However catalytic version of the reaction was limited on its efficacy and applicability. In this paper we describe the synthesis of aziridine-2-carboxylates from the reaction of hexahydro-1,3,5-triazines with alkyldiazoacetate in the presence of Lewis acid as a catalyst in high yield.



A series of our previous reports shows that N-methyleneamine equivalents could be generated *in situ* from hexahydro-1,3,5-triazines (1) in the presence of Lewis acid and reacted with various nucleophiles for the synthesis of noble aminomethylated products.^{1,6} We apply this synthetic method to prepare aziridine-2-carboxylates (2) from the reaction between N-methyleneamine equivalents and alkyldiazoacetates.⁷ When TiCl_4 or AlCl_3 was used as a catalyst ring opened product 3 was obtained in 62 and 20% yields respectively. We also have found that aziridines 2 were converted to 3 quantitatively with TiCl_4 . Among Lewis acids we tested SnCl_4 was the best for the preparation of diverse N-arylaziridine-2-carboxylates. This procedure can overcome the limitations in the similar reaction reported by Jorgensen with the $\text{Cu}(\text{OTf})_2$ catalyst.^{5b} The reaction was carried out with the same molar ratio of N-methyleneamine and diazoacetate without formation of maleate and fumarate as the self-adducts of diazoacetates. Nucleophilic addition of diazoacetate to N-methyleneamine equivalents makes an adduct as 4. Then N_2 on this adduct was released with formation of three membered ring to give aziridines. The same reactions from the chiral N-methyleneamine equivalents derived from 1,3,5-tris-(R)-, or 1,3,5-tris-(S)-phenylethylhexahydro-1,3,5-triazines yielded a diastereomeric mixture of N-phenylethylaziridine-2-carboxylates.⁸



The ratio depends on the R². When we used methyl or ethyldiazoacetate the ratio of *syn:anti* was about 2:1. With bigger alkyl group of t-butyl *syn:anti* ratio was obtained as 3:1.⁹ A little better yield without change of diastereomeric ratio was obtained with one mole equivalent of SnCl₄.¹⁰ This implies that formation of intermediate **4A** is preferred to **4B**. **4A** allows possible coordination of carboxylate with Lewis acid and minimization of steric hindrance between carboxylate and phenylethyl groups.

Table 1. Reactions of 1,3,5-trisubstituted hexahydro-1,3,5-triazine (**1**) with alkyldiazoacetate in the presence of Lewis Acid.

Substrate	R ¹	R ²	Lewis Acid	mol %	T/°C	Time (h)	Yield (%) ^a
1a	Ph	Et	TiCl ₄	20	-78	1	21 (62) ^b
1a	Ph	Et	SnCl ₄	20	-78	1	80 (5) ^b
1a	Ph	Me	SnCl ₄	20	-78	1	86
1a	Ph	Et	AlCl ₃	20	-78	1	64 (20) ^b
1a	Ph	Et	BF ₃ ·OEt ₂	20	-78	1	58
1b	2-CH ₃ -C ₆ H ₄	Et	SnCl ₄	20	-78	1	76
1c	2-CH ₃ O-C ₆ H ₄	Et	SnCl ₄	20	-78	1	50
1d	2,5-Cl ₂ -C ₆ H ₃	Et	SnCl ₄	20	-78	1	62
1e	4-F-C ₆ H ₄	Et	SnCl ₄	20	-78	1	82
R- 1f	(R)-Ph(CH ₃)CH	Et	SnCl ₄	20	-15	3	67 (67:33) ^c
R- 1f	(R)-Ph(CH ₃)CH	Et	SnCl ₄	100	-15	2	76 (64:36) ^c
R- 1f	(R)-Ph(CH ₃)CH	Me	SnCl ₄	20	-15	3	71 (61:39) ^c
R- 1f	(R)-Ph(CH ₃)CH	t-Bu	SnCl ₄	20	-15	3	57 (76:24) ^c

a. Yield of isolated pure product. Satisfactory microanalysis obtained. b. The yield of **3**. c. Diastereomeric ratio of *syn* and *anti*.

In conclusion aziridine-2-carboxylates were prepared from the reaction of hexahydro-1,3,5-triazines with alkyldiazoacetates in the presence of SnCl₄ catalyst. Further efforts are also in progress for enantioselective synthesis with chiral Lewis acid catalysts.

Acknowledgements

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References and Notes

- This paper is part 5 in the series of "Lewis acid induced N-methyleneamine equivalents". For part 4 see, H.-J. Ha, K.-H. Kang, Y.-G. Ahn and S.-J. Oh, submitted to *J. Chem. Soc. Perkin Trans. I*.
- For a comprehensive review see, Tanner, D. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599.
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- General Procedure.** To a stirred solution of 1,3,5-trisubstituted hexahydro-1,3,5-triazine (**1**) (3.0 mmol) in CH₂Cl₂ under nitrogen atmosphere was slowly added the Lewis acid at the specified temperature in the Table. After being stirred for 10 min alkyldiazoacetate (9.0 mmol) was added to it. The resulting solution was stirred at the specified temperature until all starting material was consumed on TLC. The reaction mixture was poured into ice-water. The resulting solution was neutralized with cold sat. NaHCO₃ solution. The reaction product was extracted with CH₂Cl₂. Organic layer was washed successively with water and brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude reaction product was purified by flash chromatography to give aziridine-2-carboxylates.
- The similar result as in the Table 1 was obtained from the reaction of 1,3,5-tris-(S)-phenylethylhexahydro-1,3,5-triazine and ethyldiazoacetate to yield **2S,1'S-2f** (*syn*) and **2R,1'S-2f** (*anti*) as the ratio of 64:36 with 20 mol% of SnCl₄ at -15°C.
- The ratio was determined by either isolation of each diastereomer by flash column chromatography or by ¹H NMR. See reference, 3(c).
- Similar diastereomeric ratios were obtained with Lewis acids of AlCl₃ and BF₃·OEt₂ in relatively lower reaction yields.